Expert Opinion

Unwinding Fibrosis in Peyronie's Dis[Instruction: Latest in Peyronie's Disease [PGN: Set as RRH.]]ease

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Fibrosis is defined as the excess accumulation of extracellular matrix proteins in response to chronic injury or inflammation.[1] Peyronie's disease (PD) is a fibrotic disorder affecting the penile tunica albuginea (TA), characterized by the formation of a plaque that may lead to pain, curvature, or erectile dysfunction.[2] The first observation of PD dates back to 1561, when it was reported by Fallopius and Vesalius, but it was the French surgeon to King Louis XV, Francois Gigot de la Peyronie, after whom the disease was named because of his descriptions in 1743.[3,4] Despite 276 years of knowledge of PD, the genetic basis of the disease is yet to be fully understood,[5] while much progress has been made in understanding the fibrotic process in general and in PD.[6] PD has been described to have 2 distinct phases: an acute (unstable, inflammatory) phase associated with penile pain and worsening penile deformity due to plaque development and a chronic (stable) phase typically beginning 12–18 months after disease onset with resolution of the pain and stabilization of penile plaque and curvature.[7,8] Reports have suggested the prevalence of PD to range between 0.3% and 9%.[9–11] Surgical treatment is considered to be the gold standard in patients with stable and painless PD for a period of at least 6 months to correct curvature to allow successful intercourse, despite the risks of penile shortening, erectile dysfunction, or penile numbness as well as recurrence of curvature.[12–14] Although there has been a significant unmet need to develop novel non-surgical, oral therapeutics, all the attempts have failed so far. The only non-surgical treatment that has been approved by the Food and Drug Administration for PD in men with more than 30° and less than 90° of penile curvature is collagenase clostridium histolyticum (an enzyme that specifically breaks down collagen), which needs to be administered by injection into the plaque.[15]

PD is not the only fibrotic disease that suffers from lack of successful drug development; apart from idiopathic pulmonary fibrosis for which 2 drugs have been approved (pirfenidone and nintedanib [16]), the drug

development efforts have been unsuccessful in fibrosis arena. Several review papers have discussed why and how this happened.[6,16–21] In the PD field, the lack of translational success from preclinical to clinical studies can be partly explained by the following three factors:

1. An early open-label study with tamoxifen[22] showed clinical efficacy in patients who were in early stages of the disease. However, a later placebo-controlled randomized clinical trial failed to show an efficacy where most of the patients included were at the late stage.[23] This highlights the difference between the early and late stages. Tamoxifen may not be able to reverse the existing fibrosis but may prevent the formation of new fibrotic lesion, which is accordance with preclinical evidence for tamoxifen's ability to prevent not reverse fibrosis.[24] Several preclinical studies (including ours) are aimed at developing novel medicines using preclinical models, which are limited to early stages of PD. For example, the most frequently used animal model of PD uses transforming growth factor (TGF)–beta injection into the penis of rats, and the novel drugs are administered often immediately after the TGF injection. The effect of novel drugs on established (ie, late stage) PD is difficult to test in this animal model because the plaque is known to resolve spontaneously. In other words, most of the drug development efforts have concentrated on the prevention of fibrosis rather than the reversal, whereas the clinical trials were designed to look for a reversal effect.
2. Most of the drug development efforts have been based on a single-target approach. This involves picking a single molecular target, for which small molecule ligands are developed. The best drug-like ligand is then taken through preclinical and clinical development phases. This candidate molecule then fails at phase II clinical study owing to lack of efficacy, although the results from preclinical studies including animal models have been encouraging. We are proposing that the reason behind the failure of the single-target approach in PD or fibrosis lays within the pathophysiology of fibrosis. Fibrosis is actually an aberrant form of wound healing, which is one of the strongest, most evolved and most conserved protective mechanisms in the human body.[25] The evolution has programmed several buffering systems into the wound healing mechanism; if one pathway fails, another “compensatory” pathway can take over. One can think of wound healing as a machine with several safety fall-back valves. When a single target is hit by a new drug, the machine can then activate another pathway to compensate for the lost function. It is then not surprising that these drug candidates fail in phase II clinical efficacy studies as the compensatory mechanisms are active in full force.
3. Development of novel therapeutic approaches for PD is hampered by the lack of inexpensive, reproducible, and consistent animal models that mirror the clinical aspects of the disease – most importantly curvature formation and ossification.[26] Previous models used injections of transforming growth factor-beta[27] or fibrin[28] and surgical trauma to TA[29]; however, neither significant curvature nor ossification was achieved. Repeated administration of TGF-beta is required to achieve significant curvature.[30] The Tsk genetic mouse has achieved curvature and cartilage formation but is an expensive model and the fibrosis is not limited to TA.[31] Although allograft TA transplantation in rats has been shown to achieve both significant curvature and some signs of ossification,[32] this is again a quite expensive and elaborate animal model, which

involves tissue transplantation. Most of the currently available animal models suffer from spontaneous resolution of the fibrosis, which makes long-term drug dosing studies or reversal of fibrosis attempts difficult.

Based on the aforementioned rather gloomy landscape, what can we do as preclinical and clinical scientists? Here are some suggestions:

1. Better clinical study design: Keeping in mind the notion of prevention versus reversal, we need to ensure that our clinical studies are designed to reflect the mode of action of the candidate drugs and to include the right patient for the right drug. A drug that is supposed to prevent plaque formation should only be tested on early stage patients without stable plaques, while a plaque-dissolving drug should only be tested on stable plaques. We should also ensure that any clinical trial with oral drugs should be placebo controlled particularly, given the significant variability in the natural history of the condition. It should be noted that recruitment of patients at early stage PD has always been difficult.
2. Better animal models: We need better animal models for PD that are true representatives of human pathology and that can be used for “reversal” type of studies.
3. Phenotypic screening rather than the single-target approach: Instead of the single-target approach, we can try to develop new drugs for PD using the phenotypic approach. The term phenotypic approach refers to phenotypic drug discovery (as opposed to the single target-based approach described earlier). Phenotypic drug discovery has been proven to be more effective in identifying new first-in-class drugs.[33] Phenotypic screening is thought to be more biologically and disease relevant in modulating a certain pathological phenotype opposed to an isolated pathway.[34] For this approach to drug discovery, a disease-relevant phenotype is vital.[35] In this approach, rather than picking a single target, a phenotype is selected, and the drugs are tested on the phenotype rather than the target. This approach has actually been shown to be more effective than the single-target approach when all Food and Drug Administration–approved drugs are analyzed.[33] We have recently identified a combination of phosphodiesterase type 5 inhibitors and selective estrogen receptor modulators from an in vitro phenotypic screen campaign using the myofibroblast as phenotype.[24]
4. Better understanding of PD pathophysiology: We need to understand the pathophysiology of PD better. How can an established plaque be eliminated? What are the compensatory mechanisms? What is the line that separates acute and chronic phase?

We have still much work to do on PD and all the other fibrotic diseases. Fibrosis remains a significant challenge and should not be ign[Instruction: *Conflict of Interest:* The authors report no conflicts of interest.

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